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Non-Hodgkin's Lymphoma After Liver Transplantation: Response to Chemotherapy

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An increased incidence of lymphoproliferative disorders in immunosuppressed organ transplant recipients has long been recognised. Lymphoproliferative disorders occur in 2% of orthotopic liver transplant patients. Different therapies have been used, but the optimal treatment remains unknown. Relatively little information is available on experience with cytotoxic chemotherapy. Three children who developed Burkitt-like, non-Hodgkin's lymphomas after liver transplantation are described. The disease failed to regress after initial management, which included a reduction in immunosuppression. With cytotoxic chemotherapy all three achieved complete remission, which continued 36+, 35+, and 16+ months after diagnosis. Results suggest that in selected cases chemotherapy can be safe in late-onset lymphomas appearing after solid organ transplantation.

Key words: liver transplant, immunosuppression, lymphoproliferative disease, chemotherapy

INTRODUCTION

Transplant recipients receiving therapeutic immunosuppression present a higher incidence of lymphoproliferative disease (LPD) than the general population. Appearance of the disease is related to the degree of immunosuppression required for each type of transplant and probably also to the type of immunosuppressor used. Although the frequency of LPD in these patients remains to be determined, it is estimated to be 2% of patients undergoing liver transplantation [1]. LPD may present clinically as mononucleosic syndrome, with compromised graft function, or with the appearance of solid tumors [2–4]. Epstein-Barr virus (EBV) is often implicated in the etiopathogeny of the disease, although the genome of the virus is not found in all cases despite an exhaustive search [5–7].

Treatment consists of a reduction in immunosuppression intensity, but if this measure is not accompanied by regression of the disease, particularly when there is multiorgan involvement, posterior treatment is controversial. Some authors have advocated surgical resection if possible, the addition of antiviral agents or interferon alpha in cases with concomitant EBV infection, or infusion of anti-B-cell monoclonal antibodies or radiotherapy [8–11], but despite these measures a significant proportion of these patients die from progressive or recurrent disease. The use of polychemotherapy in these circumstances has rarely been reported, although results appear to be encouraging [12,13].

Since 1985, a total of 103 liver transplants in children under the age of 16 has been performed at our center. We describe the clinical course of three of these patients who developed high-grade lymphomas during immunosuppressor treatment with cyclosporine A and who underwent anti-neoplastic polychemotherapy treatment, with maintained remission in all.

MATERIALS AND METHODS

Tumoral tissue obtained during surgery or by bone marrow aspiration was processed for optic microscopy and immunohistochemistry. Immunophenotype determination was performed using a panel of monoclonal antibodies to B- and T-cell antigens, and with polyclonal antisera to kappa (k) and lambda (l) chains. LPD was classified according to the criteria established by Nalesnik

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[14]. Clonality of the tumor was assessed by determining kappa/lambda ratio and considered monoclonal if k:l > 5 or l:k > 3 [15].

In order to determine disease extension, patients were assessed by detailed clinical history, complete physical examination, appropriate imaging studies, and bone marrow (BM) and cerebrospinal fluid (CSF) examinations. According to the results, patients were staged following Murphy's classification [16]. Polychemotherapy was administered according to the LMB89 therapeutic protocol [17].

Briefly, patients were assigned to three different risk groups, which included: Group A (stages I,II) who received two courses of therapy with cyclophosphamide (CPM), vincristine (VCR), adryamycin (ADR), prednisone; Group B (stages III, IV with BM involvement <70%) who received five courses of polychemotherapy based on high-dose methotrexate (MTX) 3 g/sq m, CPM, ADR, and cytosine arabinoside (Ara-C) in continuous infusion with CNS prophylaxis with MTX, Ara-C, Hydrocortisone; Group C (stage IV with CNS or BM involvement >70%, or both) who received seven courses of polychemotherapy with an induction regimen similar to the former with the exception of MTX administered at 8 g/sq m and consolidation with Ara-C g/sq m and etoposide and triple intrathecal treatment with cranio-spinal irradiation if CNS involvement is present.

Case 1

A 7-year-old girl underwent liver transplantation in May 1987, for cirrhosis secondary to active chronic hepatitis. She received immunosuppressor treatment with cyclosporine A until May 1992 (60 months post-transplant) when she developed intestinal occlusion.

Imaging studies revealed multiple tumoral masses in the jejuno-ileon, enlarged mesenteric lymph nodes, bilateral ovary infiltration, and three nodules in the right hepatic lobe. Surgery was performed with resection of the intestinal tumoral masses and posterior end-to-end anastomosis. Histologic study showed the presence of a high-grade B-cell (CD20+), Burkitt-like lymphoma, which was monomorphous and monoclonal (k:l > 5). No serologic evidence of EBV infection was found.

Extension study showed the presence of mediastinal lymphadenopathy, with no BM or CSF involvement (stage III).

Despite the progressive reduction in cyclosporine A until complete withdrawal, the abdominal and mediastinal disease continued to progress, and chemotherapy was started according to LMB89 protocol- Group B. The girl achieved complete remission after the third course of therapy and is currently disease-free 36 months after diagnosis.

At the time of the last treatment course, she presented a moderate alteration in liver tests and the histologic presence of rejection was verified. Immunosuppression with cyclosporine was resumed and is currently maintained, with normal function of the transplanted organ.

Case 2

A 5-year-old boy underwent liver transplantation in September 1989, owing to biliary atresia. He received immunosuppressor treatment with prednisone and cyclosporine A initially, followed by cyclosporine A alone until June 1992 (33 months post-transplant) when a 15 × 12 cm abdominal mass was observed in the right iliac fossa together with a 2 cm diameter nodule in the right hepatic lobe and bilateral nephromegaly. Bone marrow study revealed 70% infiltration by atypical Burkitt-like monomorphous B cells with a k:l ratio >5. Viral serologic studies demonstrated active primary EBV infection (positive viral capside antigen IgM). Cyclosporine was suspended and owing to tumor progression, chemotherapy according to LMB89 protocol was initiated -Group C.

The patient's clinical course was complicated initially with the appearance of a tumor lysis syndrome treated successfully with support measures. He later presented repeated episodes of febrile neutropenia with blood culture positive in 1 episode to *Staphylococcus epidermidis,* which responded to adequate antibiotic therapy.

The patient achieved complete remission following the second course of treatment and remains disease-free 35 months after the diagnosis of lymphoma. When chemotherapy was completed, immunosuppressor treatment with cyclosporine was restarted due to the appearance of biochemical and histologic signs of rejection, and liver function is currently normal.

Case 3

An 11-year-old boy with cirrhosis secondary to autoimmune hepatitis received a liver transplant in January 1989, and he was treated initially with an immunosuppressor regimen consisting of prednisone and cyclosporine A and subsequently with cyclosporine A alone. In December 1993 (58 months post transplant), he presented a 4.5 × 5 cm left submandibular mass; histologic study revealed a high-grade, B-cell polyclonal Burkitt-like lymphoma. Extension study showed no disease at other sites (stage I). Immunosuppression was progressively reduced until withdrawn completely; rapid regrowth of the cervical mass was observed, and thus chemotherapy with LMB89 protocol-Group A- was started after a second tumor resection.

The patient attained complete remission after the first course of treatment and remains disease-free 16 months post-diagnosis. After completion of treatment and despite the prompt resumption of immunosuppression, progres-

sive dysfunction of the graft was observed and a re-transplant was performed in October 1993. The extracted organ showed chronic rejection without evidence of neoplastic infiltration. Viral studies failed to demonstrate viral infection either in peripheral blood or in the extirpated organ. Correct liver function is currently maintained 6 months after re-transplant.

DISCUSSION

Lymphoproliferative disorders constitute a frequent complication in transplant recipients undergoing immunosuppressor therapy. These disorders have been described with an approximate frequency ranging from 1% to 13% of cases, with the highest incidence coresponding to heart- and lung-transplanted patients [18–20]. This greater incidence is attributable to the degree of therapeutic immunosuppression required to maintain graft function [21].

Starzl [15] described the appearance of lymphoproliferative lesions in three of 129 liver transplant recipients treated with cyclosporine A and prednisone over a period of 4 years, which represents a frequency of 2%. Other authors have reported a similar frequency [22–23].

LPD may present as a spectrum of disorders ranging from mononucleosic syndrome to true lymphomas. The most frequent presenting symptoms include fever, tonsillitis, and lymphadenopathy. More than half the patients described presented disease involvement of two or more organs, the most frequently affected being the small intestine, liver, and kidneys.

Clonality studies reflect a spectrum as heterogeneous as clinical presentation, oscillating between polyclonal lesions that regress rapidly when immunosuppression is withdrawn and monoclonal lesions or poly- and monoclonal mixed lesions. Although the former present more frequently in relatively early stages post-transplant, polyclonality, as in our third patient, has been demonstrated even in late-onset disease and similar to high-grade, Burkitt-like lymphoma or immunoblastic sarcoma [24]. It has not been possible to establish a correlation between the presence or absence of monoclonality and disease aggressivity, although monoclonal forms appear to follow a more rapidly progressive course.

In all cases, if the response to reduction in immunosuppression is not complete, mortality is very high in all forms of the disease.

Concomitant EBV infection can be demonstrated in most cases of post-transplant LPD, and the most frequent form in transplanted children is the primary infection [5]. Only one of our patients showed evidence of infection, although an exhaustive search for the virus genome in tumoral tissue was not carried out.

Our cases presented clinically as rapidly evolving high-grade, B-cell lymphomas in relatively late post-transplant stages, and response to immunosuppression reduction was not demonstrated in any case. All three presented a rapidly progressive course and thus were offered antineoplastic chemotherapy based on previous experience of similar toxicity and tolerance to chemotherapy in patients undergoing organ transplantation compared with the general population [25,26].

Although our results may suggest an effective therapy in these patients, caution should be advocated in treating them with chemotherapy alone. In localized disease, surgery and a reduction in immunosuppression may be curative, but in progressive disease, chemotherapy may be considered if regression on withdrawal of immunosuppression is not observed. However, the precise role of chemotherapy has not been established. In our experience, the degreee of toxicity of the regimens used is similar to that of immunologically competent pediatric patients with non-Hodgkin's lymphomas, and problems derived from myelosuppression have been safely overcome with the usual support measures. Our results concur with those of other authors who have used antineoplastic chemotherapy to treat these patients and with results obtained in patients with lymphomas and HIV infections [27,28].

It is noteworthy that during chemotherapy, the degree of immunosuppression obtained was sufficient in the three patients to preserve normal function of the transplanted liver and that immediately after completion of therapy, rejection was observed in all. This observation differs from the experience of other authors who have demonstrated the appearance of tolerance following chemotherapy regimens of similar intensity [29]. The only difference with patients previously reported is that those patients were adults. Perhaps the fully competent immunological system of these children contributes to our observation.

In conclusion, our experience suggests that chemotherapy can be useful in selected cases of late-onset immunosuppression-associated lymphomas and that toxicity is similar to that of other patients not previously immunosuppressed who undergo similar regimens.

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